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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/845,511	Thomas
Examiner	**Art Unit**
Dave Nguyen	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Aug 22, 2002*

2a) X This action is **FINAL.** 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *17-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) X Claim(s) *17-35* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) X The drawing(s) filed on *May 12, 2003* is/are a) X accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1. Notice of References Cited (PTO-892)
2. Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. X Information Disclosure Statement(s) (PTO-1449) Paper No. #11
4. Interview Summary (PTO-413) Paper No.
5. Notice of Informal Patent Application (PTO-152)
6. Other:

The response filed May 12 , 2003 coupled with the second copy of the IDS have been entered and considered. The response has been considered fully and is found partially persuasive but is not found fully persuasive for patentability of the full breadth of the claimed invention. The following scope rejection under 35 USC 112, first paragraph reflects the consideration of the response.

Claims 17-35, to which the following ground of rejection remain applicable, are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

The method as recited in any of the base claims 17, 22 and 27, wherein the route of administration of the claimed DNA vaccine is limited to intradermal administration or intramuscular administration, does not reasonably provide enablement for a treatment and/or prevention of any cardiovascular disease in any human or animal as set forth in claim 31, and for any other route of administration that must exhibit a vaccine effect in any human or large animal or mammal . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Nature of the invention, breadth of the claims, the amount of direction or guidance presented

The claimed invention was based on a hypothesis that the CETP-expressing transgenic murine model is an art-recognized model for atherosclerosis, and that increased levels of CETP activity may be predictive of increased risk of cardiovascular disease. The as-filed application further states that endogenous CETP activity is thus an attractive therapeutic target for modulating the relative levels of lipoproteins to prevent or inhibit the development of or to promote regression of cardiovascular diseases such as atherosclerosis. On the basis of this hypothesis, applicant 's claimed invention is mainly directed to employed plasmid-based vaccine expressing a CETP peptide so as elicit a therapeutic and/or prophylactic effect in inhibiting the endogenous CETP activity thereby preventing or treating any cardiovascular disease in any animal or a human subject at risk of having a cardiovascular disease or a cardiovascular disease bearing patient.

The application further states provides guidance and/or factual evidence showing a rabbit model for atherosclerosis, wherein an intramuscular injection of a plasmid-based vaccine expressing a CETP peptide elicits an increased immune response that effects a reduction of endogenous CETP, and a reduction of atherosclerotic lesions in rats fed with cholesterol.

On the basis of applicant's showing of the hypothesis using transgenic mice model, which illustrates that an increased levels of CETP activity may be predictive of increased risk of cardiovascular disease, and of applicant's rabbit model for atherosclerosis, applicant contemplates and claims that any of applicant's

claimed plasmid based vaccines can be used to provide a therapeutically or prophylactically cardiovascular benefit in any animal or a human subject or patient.

The state of the prior art, the unpredictability of the art, and the relative skill of those in the ATHEROSLEROSIS-therapy art.

With respect to the state of the prior art, no prior art from the time the invention was made until now (about 6 years after the effective filing date of this instant application) has demonstrated that any DNA vaccine, has been successful in treating an atherosclerotic patient in the real world (human patients, primates and/or pets) as intended by applicants at the time the invention was made.

More specifically as to the nature of the invention which claims that DNA plasmid based vaccine expressing a CETP peptide can be a therapeutically or prophylactically master drug to treat any animal or human at risk or having a cardiovascular disease, which disease and its corresponded lipoprotein metabolism is well-known in the prior art as being complex and not correratable among animal species. For example, Gordon (The New England J. of Medicine, Vol. 321, 19, pp. 1311-1316, 1989) indicates that while higher HDL levels associate with higher rates of coronary disease such as atherosclerosis, neither our present understanding of lipid metabolism nor the association provides assurance that intervention to raise levels of HDL would be beneficial (page 1134, column 1, second paragraph), and that the only way those skilled in the art can confidently apply what we have learned about HDL to the amelioration and prevention of coronary disease is to apply a real working protocol or trial in atherogenic patient with low HDL (page 1315, first column, last paragraph).

In addition, Luc *et al.* (Database Embase, AN : 97251152, Sang Trombose Vaisseuax, Vol. 9/4, pp. 206-212), states (abstract) :

> The incidence of coronary heart disease is inversely correlated to a high density lipoprotein (HDL) concentration. However, the direct responsibility of HDL in the appearance and the development of atherosclerotic lesions is hypothetical [*emphasis added*]. The biological function of HDL in reverse

cholesterol transport from peripheral tissues to the liver is an argument in favor of direct protective role of HDL. However, the absence of atherosclerosis in a few subjects with a very low HDL level due to mutations in the apolipoprotein (apo) A1 gene or LCAT gene suggests that HDL such as they appear in normolipidemic subjects are not indispensable in preventing the appearance of atherosclerosis....Furthermore, a hypoalphalipoproteinemia is frequently concomitant to other metabolic abnormalities such as a high level of VLDL remnants and a small size of LDL, abnormalities know as atherogenic factors.

Assmann *et al.* (J. of Cardiovascular Pharmacology. 16/Suppl. 9 (S15-S20). 1991) reaffirms the complexity of atherosclerosis and indicates that while it is well recognized within the scientific community that HDL plays an important role in the atherosclerotic process, "the complexity of the processes involved in HDL metabolism makes it likely that besides HDL cholesterol reductions that **predispose** to arteriosclerosis, there will also be those that are not associated with a particular risk" (abstract, *emphasis added*), and that "the detailed further analysis of genetic and secondary HDL deficiency syndromes as well as the identification of the precise biochemical mechanisms underlying reversed cholesterol transport remain a challenge in the understanding of the role of HDL in atherosclerosis" (abstract). In addition, in a review article coauthored by Stein not only questions the validity of extrapolating the results from the transgenic rabbit model to humans (abstract, page 292 bridging page 293), but also indicates that atherosclerosis is a multistep process, the various components of HDL can intervene at different states, such as induction of monocyte adhesion molecules, prevention of LDL modification an d removal of excess cholesterol by reverse cholesterol transport, and that while transgenic technology has provided a model for atherosclerosis, the extent to which pharmacological attempts of increasing HDL levels so as to **prevent human atherosclerosis needs further evaluation** (abstract).

The evidentiary support as indicated above not only expresses doubts as to applicant's contemplation and claim of therapeutic application of any DNA plasmid based vaccine expressing any CETP peptide as a magic bullet to treat any *animal or human in need of a treatment for a cardiovascular*

disease, let alone subject at risk of having a cardiovascular disease, but also clearly indicates that while transgenic technology may be valuable in studying atherosclerotic process and **various risk factors that contribute to the process**, the transgenic model and the exemplified rat models wherein an intramuscular injection of the claimed DNA vaccine results to only a reduction of atherosclerotic lesions in rats fed with cholesterol. not the same as therapeutic application of CETP expressing plasmid based vaccine in treating any animal or human so as to provide a cardiovascular benefit such as a preventive treatment of any cardiovascular disease as contemplated by applicant at the time the invention was made.

Notwithstanding that fact that more than 6 years after the effective filing date of the claimed invention, there is no evidentiary support from any prior art as a result of examiner's exhaust prior art search, which indicates that CETP peptide expressing plasmid based vaccines can be used therapeutically or prophylactically in treating any real world-animal or human at risk of or having a cardiovascular disease. the following prior art further teaches that an extrapolation from mice or rabbit models (not limited *per se to* transgenic models as interpreted by applicant in the latest response) to a reasonable enablement of a prophylactic or therapeutic application of CETP peptide expressing plasmid based vaccines in treating a human remains complex and unpredictable.

1/ Stedronsky, Biochimica et Biophysica Acta – Lipids and Lipid Metabolism, 1210/3, 255-287, 1994, states (abstract):

> Not all of the animal testing which has been used to measure hypocholesterolemic effects is of equal reliability or applicability to man. Work done in the rat and rabbit needs to be interpreted with caution...the profile of lipoproteins in plasma in the rat differs from that in the human in that the rat carries most of its cholesterol in HDL, while the human carries a much higher proportion in LDL. The rat liver rapidly clears lipoprotein remnants from the circulation. The rat also lacks an active cholesteryl ester transfer protein, CETP. In view of these differences, great care must be applied to extrapolation of these data and conclusions from the rat to man.

2/ Even in 2000, McNamara in the review article of Biochimica et Biophysica Acta 1529, 2000, 310-320 states (page 311, column 1 bridging column 2):

> The plasma cholesterol response in dietary cholesterol is highly variable across and within animal species. While rabbits are highly susceptible to dietary cholesterol, rats and dogs exhibit little change in plasma total cholesterol even with high doses of dietary cholesterol. Non-human primates are highly variable in their responses to dietary cholesterol and in many species it is only with extremely high doses of dietary cholesterol (0.5-2 mg/kcal or 1250-5000 mg/2500 kcal) that hypercholesterolemia and atherosclerosis can be induced. Another complication of animal studies is that most animal species have a significantly different plasma lipoprotein profile compared to humans. Whereas humans have low density lipoprotein (LDL) cholesterol as the predominant plasma lipoprotein, most animal models have high density lipoprotein (HDL) cholesterol as the major fraction. The species differences in the response to dietary cholesterol, the use of pharmacological doses of dietary cholesterol in many studies, and differences in the plasma lipoprotein profile make extrapolations from the results of animal feeding studies to human health recommendations difficult, if not impossible.

3/ Even with respect to applicant's contemplation of just the disclosure of CETP expressing transgenic mouse and the exemplified rats having a reduction of an atherosclerotic lesion being reasonably extrapolated to the **preventive effect of CETP peptides in humans in reducing development of atherosclerosis,** the Stein reference (Atherosclerosis, 144, pages 285-301, 1999) further reaffirmed the doubts expressed by other skilled artisans including Stedronsky and McNamara by stating (abstract):

> The findings that LCAT overexpression in rabbits was **atheroprotective** in contrast to increase in atherosclerosis in h [human] LCAT tg [transgenic] mice, which was only partially corrected by CETP expression, call for some caution in the extrapolation of the results from transgenic animals to humans.

As the result of the evidentiary support as cited above, those skilled in the art at the time the invention was made, who are clearly aware of the fact that **rat or rabbits** a) exhibit little change in plasma total cholesterol even with high doses of dietary cholesterol; b) do not carry an endogenous level of an active cholesteryl ester transfer protein, CETP, as compared to humans, c) carry most of its cholesterol in HDL, while the human carries a much higher proportion in LDL, and d) rapidly clears lipoprotein remnants from the circulation as compared to humans, would have to engage a undue experimentation to reasonably extrapolate from the results observed in the animal mouse or rabbit models provided in the prior art and the as-filed application to the subject matter being sought in the presently pending claims, which subject matter is to provide any cardiovascular benefit to any animal or human at risk of or having a cardiovascular disease.

To further support the lack of reasonable predictability in using animal models for atherosclerosis, and to support the presence the conflicting data coming out at the time the invention was made, particularly with regard to applicant's notion that an increased levels of CETP activity may be predictive of increased risk of cardiovascular disease, and that anti-CETP activity in an animal or a human is an effective therapeutic or prophylactic application of providing a cardiovascular benefit, Hayek *et al.*, J. Clin. Invest., 96, pp 2071-2074, 1995, demonstrated that expressing of CETP **protects against atherosclerosis in hypertriglyceridemic mice.**

The doubts as expressed in Hayek *et al.* are further reaffirmed by the following skilled artisans:

4/ With respect to a human study relied upon by applicants the benefit of not having CETP in the circulation system of a human subject, which is based on a preliminary study on some of the first CETP-deficient Japanese patients who do not develop atherosclerosis, *e.g.*, an earlier study disclosed in Inazu et al., N. Engl. M. Med., 323: 1234-1238, 1990, Zhong et al., J. Clin. Invest, 97:2917-2923, 1996, Hirano et al., Arterioscler. Thromb. Vasc. Biol., 17:1053-1059, 1997, both tested the hypothesis by performing large

population-based studies in Honolulu and Japan, and come up the completely different conclusions by indicating that **low CETP plasma levels due to a common genetic polymorphism as well deficiency of CETP are associated with an increased incidence of coronary heart disease.**

2/ Kunitake et al., J. Lipid Res. 33:1807-1816, 1992, and Newnham et al., Biochim. Biophys. Acta, 1044:57-64, 1990, both teach that contrary to the hypothesis presented by other skilled artisans that CETP activity leads to decreased plasma levels of HDL cholesterol and increased LDL cholesterol. CETP can also promote dissociation of apoA-I from HDL, generating pre-β-HDL particles, which together with the enhanced transport of CE to triglyceride-rich lipoproteins, may facilitate reverse cholesterol transport.

3/ Foger *et al.*, The J. of Biological Chemistry, Vol. 274, 52:36912-36920, 1999, also surmised the complexity and unpredictable factors in elucidating art-recognized model for atherosclerosis:

> Furthermore, the elucidation of the role that CETP plays in atherogenesis has proved a major challenge. Animal and human studies have provided evidence supporting its function both as a pro-atherogenic, and anti-atherogenic factor. These conflicting data suggest a complex metabolic role for CETP *in vivo* CETP activity can lead to decreased plasma levels of HDL cholesterol and increased LDL cholesterol, a change in the lipoprotein profile that may promote atherogenesis. However, CETP can also promote HDL remodeling with generation of pre-β-HDL particles, which together with the CETP-mediated enhanced transfer of CE to triglyceride-rich lipoproteins, can facilitate reverse cholesterol transport. **Ultimately, the effect of CETP on atherosclerosis may depend on which of these functions is most effective in altering the dynamics of cholesterol transport from HDL to the liver, which in turn may depend on the metabolic status of the animal model (*i.e.*, the presence of hypertriglyceridemia, LDL receptor, or apoE deficiency).** (page 36916, column 2, middle of second paragraph).

Foger *et al.* then provides definitive *in vivo* evidence supporting the proposed anti-atherogenic role of CETP in facilitating HDL-mediated reverse cholesterol transport:

> Our findings in these mouse models have a counterpart in human patients. Like LCAT-Tg mice, patients with CETP deficiency accumulate apoE-rich HDL1 that exhibits abnormal functional properties with decreased cholesterol efflux and delayed clearance of CE transported with HDL. Furthermore, HDL isolated from CETP-deficient patients fails to protect macrophages from foam cell formation. **As in our animal models, the consequence of CETP deficiency, in at least a subset of CETP-deficient patients, is enhanced atherosclerosis.** (page 36919, column 1).

> We conclude that CETP expression reduces atherosclerosis in LCAT-Tg mice in restoring the functional properties in LCAT-Tg mice by restoring the functional properties of LCAT-Tg mouse HDL and promoting the hepatic uptake of HDL-CE. These findings provide definitive *in vivo* evidence supporting the proposed anti-atherogenic role of CETP in facilitating HDL-medicated reverse cholesterol transport and demonstrate that CETP expression is beneficial in pro-atherogenic states that result from impaired reverse cholesterol transport (abstract, also page 36919, column 1, *emphasis added*).

6/ More specifically as to pitfalls of transgenic animal models, the complexity of HDL-cholesterol and its role in anti-atherosclerosis, and the importance of CETP with respect to its role in reverse cholesterol transport system, Yamashital *et al.*, Atherosclerosis, 152:271-285, 2000, states:

> The deficiency of CETP causes various abnormalities in the concentration, composition, and function of both HDL and low density lipoprotein (LDL). The significance of CETP in terms of atherosclerosis had been controversial. However, the in vitro evidence showed large CE-rich HDL

particles in CETP deficiency are defective in cholesterol efflux. Similarly, scavenger receptor BI (SR-BI) knockout mice **show a marked increase in HDL-cholesterol but accelerated atherosclerosis** in atherosclerosis-susceptible mice. Recent epidermiological studies in Japanese-Americans and in Omagari area where HALP [hyperalphalipoprotienemia] subjects with the intron 14 splicing defect of CETP gene are markedly frequent, have demonstrated in an **increased incidence of coronary atherosclerosis in CETP-deficient patients** (abstract).

Serum HDL-cholesterol level does not correlated with anti-atherogenicity (page 273, column 2).

These animal models have provided a very good tool for assessing the physiological roles of molecules. However, there are difficulties in drawing conclusions on the atherogenicity of each molecule from studies using animal models such as mice, of which the lipoprotein metabolism is quite different from that of humans. One has to assess the species differences in lipoprotein metabolism. Furthermore, these studies may establish a notion that serum levels of HDL-cholesterol do not necessarily correlate with the degree of protection from atherosclerosis. **It may be crucial to assess the efficiency of reverse cholesterol transport system irrespective of serum HDL-cholesterol levels, since HDL particles become 'dysfunctional' due to the impairment of this system.** (page 276, column 1).

The frequency of CETP deficiency was also reduced in subjects over 80 years of age compared with those under 80 years...Moreover, ultrasound examination of carotid arteries demonstrated higher atherosclerotic scores in hyperalphalipoproteinemic CETP-deficient subjects than in control CETP-positive subjects (page 279, column 2, last paragraph).

However, a careful prospective study on the atherogenicity of patients with CETP deficiency is necessary to drawn conclusions. It is also essential to determine clearly whether the increase in

HDL-cholesterol may protect against or rather accelerate atherosclerosis in CETP-deficient patients (page 280, column 2).

To the authors' current knowledge, the level of serum HDL may not necessarily imply the functional aspects of HDL particles. HALP may be a condition of an impaired reverse cholesterol transport system. The 'dysfunctional HDL particles' produced by the impairment of molecules involved in reverse cholesterol transport system may lead to the acceleration of atherosclerosis in humans. For this reason, CETP inhibitors may not be a good tool for the purpose of treatment of atherosclerosis. Taken together, it may be important to establish a strategy to assess the efficiency of reverse cholesterol transport system rather than merely determining the level of HDL-cholesterol. (page 280 bridging page 281).

On the basis of the totality of the art of record, the complexity of the nature of the invention, the lack of an art-recognized model for atherosclerosis, the doubts expressed in the art of record as to applicant's reliance on the inhibition of endogenous CETP circulated in an intended subject such as human for providing any and/or all cardiovascular benefit (see claim 31, *emphasis added*) , a skilled artisan would not have recognized that the as-filed specification provides a reasonable enablement to the claimed invention within the context of DNA vaccine for treating any atherosclerosis in any animal or human, and that a skilled artisan would not have to engage an undue experimentation to reasonably extrapolate from applicant's disclosure to any therapeutic or prophylactic application of applicant's claimed invention in treating any animal or human so as to provide any cardiovascular benefit.

Even if assuming for argument that applicant's rabbit model, wherein an intramuscular injection of a DNA plasmid based vaccine can be reasonably extrapolated to any cardiovascular benefit within applicant's contemplation from the as-filed specification, the state of the prior art of DNA vaccine remains

unpredictable at the time the invention was made due the lack of reasonable correlations among the animal species with respect to *routes of administrations, and the problems of transient in vivo transient gene expression from plasmid vectors as the result of having a particular route of administration being employed.*

The state of the art exemplified in McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees.... and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs, *emphasis added*). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

More specifically to the limitations of the rat models, Whitlock *et al.* (J. Clin. Invest., 1989, IDS) teach that "an unexpected finding of this study was the TG-rich nature of these rabbits' HDL and LDL", that "this reflects in part the high level of transfer activity in this species, since with CETP inhibition, the HDL composition came to resemble that of nonfasting rabbits" and that "stress-mediated hypertriglyceridemia may also have contributed to this TG [tryglyceride] enrichment".

In addition, major considerations for any gene transfer or DNA therapy protocol involve issues that include:

1/ The type of vector and amount of DNA constructs to be administered:

2/ The route and time course of administration, the sites of administration, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

3/ What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, the protein being produced, and the disease being treated.

More specifically, Anderson summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). In addition, Verma *et al.* states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, column 1), and that one major obstacle to success has been the ability to deliver genes efficiently and obtain sustained expression (page 239, column 3).

Furthermore, the state of the art of Shih *et al.* (Molecular Medicine Today, 1, 8, pp. 364-72, 1995) teach that atherosclerosis is a highly complex disorder with multiple genetic and environmental influences (abstract), that "it is important to note that the mouse has significant limitations for atherosclerosis research", that "there are, for example, several fundamental differences in lipoprotein metabolism between mice and humans", and that "results from studies with mice should be extrapolated to humans with caution" (page 371, column 1). In addition, Feldman *et al.* (J. Clinical Investigation, 95, 6, 2662-71, 1995) teach "Extrapolation of findings reported here for the neointimal lesion induced by arterial injury in the hypercholesterolemic rabbit, to the atherosclerotic lesion responsible for arterial narrowing in humans must

be undertaken with some caution. Certain features of advanced primary atherosclerotic lesions in humans are not typical features of lesions generated in this particular animal model". It is not apparent as to availability of DNA plasmid vectors that would generate and produce an effective amount of recombinant B cell CETP epitopes is reasonably extrapolated to any and/or all routes of administrations other than intramuscular injection, particularly since *in vivo* DNA expression is transient and depends of many essential factors including a route of administration, as clearly indicated in the art of record.

Thus, in view of the unpredictability of *in vivo* DNA transfer techniques so as to generate a therapeutically relevant response even in a DNA plasmid based immunization method, as expressed in the art of record, the lack of correlation between an efficacy in a high fat induced rat model and that of a mammal predisposed to atherosclerosis and/or having an atherosclerotic plaque and/or lesion, one skilled in the art would not, without any undue experimentation, be able to reasonably extrapolate from the disclosure of the claimed invention to the subject matter being sought in the claims. Furthermore, the breadth of the claimed invention not only encompasses any animal but also is directed specifically to any human subject at risk of or having a cardiovascular disease (see claim 31, *emphasis added*) However, in view of the reasons set forth above, the lack of teachings regarding as to what are exactly operative embodiments other than intramuscular injection, the doubts expressed by the totality of the art of record, the problems of *in vivo* transient expression, the lack of reasonable correlation between DNA immunization in a murine model and that of other mammals (specifically with regard to routes of administration other than intramuscular injection or gene gun's immunization), the lack of reasonable correlation between one specific epitope of a specific pathogen used in a DNA immunization method and any other specific epitope of any other protein used in a DNA immunization, and the lack of reasonable correlation between applicant's guidance and/or working examples and claims that encompass broadly any therapeutic or prophylactic application of any plasmid based vaccine expressing a CETP peptide in any animal including a human subject, one of skilled in the art would not be able to reasonably extrapolate, without any undue experimentation, from the basis of applicant's disclosure and the state of the prior art to the full breadth of applicant's claimed invention.

Based on the findings above-that all of the Wands factors other than the level of skill in the art weigh in favor of nonenablement: It is the examiner's position that the specification does not provide adequate guidance to enable practice of the claimed invention without undue experimentation.

To the extent that applicant's response is applicable to the remaining issues as set forth in the above stated rejection, the response is not found persuasive because of the reasons set forth in the stated rejection and the following reasons.

Issue of the examiner's indication of the CETP-transgenic mouse

Applicant asserts that the examiner incorrectly interpreted the exemplified working example 1 for the CETP transgenic mouse. In response, the examiner maintains that the stated office action clearly acknowledges that in addition to the disclosure of the CETP transgenic mouse provided in the prior art.

> The application further states provides guidance and/or factual evidence showing a rabbit model for atherosclerosis, wherein an intramuscular injection of a plasmid-based vaccine expressing a CETP peptide elicits an increased immune response that effects a reduction of endogenous CETP, and a reduction of atherosclerotic lesions in rats fed with cholesterol.

As such, there is no mistake in the stated office action in stating the nature of the invention and applicant's disclosure of factual evidence and data relevant to the claimed invention. The thrust of the stated office action is that neither the CETP expressing mouse nor applicant's rabbit models wherein an intramuscular injection of the claimed DNA vaccine generates only a reduction of altherosclerotic lesion can be used to reasonably extrapolate to the full breadth of the claimed invention as set forth in claim 31 and to the use of the claimed DNA vaccine for any route of administration other than intradermal or intramuscular injection in a representative number of species of animals and human patients.

Issue of the use of the Anderson and Verma References in the stated office action

Applicant asserts and/or implies that the stated office action only relies upon the Anderson and Verma references and use in the references in the context of gene therapy whereas the claimed invention

is drawn to DNA vaccine of using a DNA expressing a B cell epitope of CETP. In response, the stated office action in no way is relied upon only Anderson and Verma within the context of gene therapy for presenting the outstanding issues as set forth above. The stated office action when read as a whole not only provide numerous references which discuss specifically the nature of the claimed invention, *e.g.*,

Gordon (The New England J. of Medicine, Vol. 321, 19, pp. 1311-1316, 1989), Luc *et al.* (Database Embase, AN : 97251152, Sang Trombose Vaisseuax, Vol. 9/4, pp. 206-212), Assmann *et al.* (J. of Cardiovascular Pharmacology, 16/Suppl. 9 (S15-S20), 1991), Stein reference (Atherosclerosis, 144, pages 285-301, 1999), Stedronsky, Biochimica et Biophysica Acta – Lipids and Lipid Metabolism, 1210/3, 255-287, 1994, Kunitake et al., J. Lipid Res. 33:1807-1816, 1992, and Newnham et al., Biochim. Biophys. Acta, 1044:57-64, 1990, McNamara in the review article of Biochimica et Biophysica Acta 1529, 2000, 310-320, Hayek *et al.*, J. Clin. Invest., 96, pp 2071-2074, 1995, Inazu et al., N. Engl. M. Med., 323: 1234-1238, 1990, Zhong et al., J. Clin. Invest. 97:2917-2923, 1996, Hirano et al., Arterioscler. Thromb. Vasc. Biol., 17 1053-1059, 1997, Foger *et al.*, The J. of Biological Chemistry, Vol. 274, 52:36912-36920, 1999, Yamashital *et al.*, Atherosclerosis, 152:271-285, 2000, McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999), *et al.* (Molecular Medicine Today, 1, 8, pp. 364-72, 1995), Feldman *et al.* (J. Clinical Investigation, 95, 6, 2662-71, 1995).

The Anderson and Verma further substantiate the complexity and a required further undue experimentation in practicing the full breadth of the claimed invention. The claimed invention requires the use of a DNA transfer vector to carry an expression cassette encoding a gene segment coding for a B cell epitope of CETP and a gene *in vivo* transfer protocol that must be able to express a sufficient amount of the B cell epitope of CETP in order to the elicit a preventive and/or therapeutically relevant effect as embraced by the claimed invention. As such and to the extent that major issues in a DNA therapy protocol involve main issues such as

1/ The type of vector and amount of DNA constructs to be administered:

2/ The route and time course of administration, the sites of administration, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

3/ What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

Anderson and Verma coupled with above cited references, when read as a whole, do teach and further substantiate the remaining obstacles of DNA therapy which have not been overcome by a skilled artisan at the time the invention was made. Thus applicant's assertion as to the irrelevance of the disclosure of the CETP transgenic mouse and the issues of problems associated with *in vivo* gene expression as set forth in Anderson and Verma is not found persuasive. Applicant's relies upon the CETP transgenic mouse as the main basis and/or hypothesis to invent the claimed invention wherein example 1 was conducted, and as such, and to the extent that there are doubts expressed in the art of record as to the CETP being the solely causing agent for any cardiovascular disease, the transgenic model and/or working examples using rabbit models are relevant in assessing applicant's nature of the claimed invention and its reasonable predictability at the time the invention was made. Insofar as *in vivo* expression of a B cell epitope carried by a DNA vector coupled with a route of administration is required to practice the claimed invention, the issues of the use of a particular vector, promoter, route of administration and an *in vivo* model as set forth not only in the general art of Anderson and Verma but also in McCluskie *et al.* are relevant and important to the practice of the full breadth of the claimed invention.

Issue of Wands factors and/or citations of court decisions on pages 3-7 of the response

In this regard, the examiner respectfully maintains all of the Wands factors have been considered and the stated rejection remains proper because of the reasons set forth above, since none of the court decisions are related specifically to any of the remaining outstanding issues as set forth in the stated rejection.

Issues of the citation of US Pat Nos 6,284,533, 6,410,022, and 6,555,113

Other that US 6,555,313 which was examined by the examiner, none of the claims in the '533 and

'022 patent are drawn to the DNA vaccination methods as broadly claimed in claim 31. As such, the issued claims are only relevant to the extent that the claimed invention is drawn to the preambles as set forth in claims 17, 22, and 27. Even with the '113 patent, the patent claims are directed to DNA immunogenic compositions and thus do not constitute as substantial evidence to overcome the lack of reasonable predictability in practicing the full breadth of the claimed invention when taken into consideration of the nature of the claimed invention, the state of the totality of the prior art, the presence of working examples and lack thereof, the level of a skilled artisan, the full breadth of the claims, the guidance provided by the specification, the level of the predictability of the claimed invention.

Issues of applicant's assertion that the office action requires that only operative embodiments can be present in the claims to have patentability (page 6)

In response, the stated above office action does not require in any way that applicant must provide sufficient guidance and/or evidence to practice every possible claimed embodiment as embraced by the claimed invention. The issue is that the claimed invention claims that the claimed DNA vaccine can be used to treat any possible cardiovascular disease by using any route of administration of the claimed DNA vaccine. However, the totality of the art of records does not appear to support applicant's contemplation and a such, the full breadth of the claimed invention is not enabling at the time the invention was made. To further support the examiner's position, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23, 30 USPQ2d 1438, 1445 & n23 (Fed Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514, [footnote omitted].

On this record coupled with doubts expressed in the art of record regarding applicant's disclosure and/or working examples, it is apparent that the specification provides no more than a plan or invitation for those skill in the art to experiment the concept of employ B-cell epitope of

CETP coupled with recombinant DNA *in vivo* transfer techniques to treat and/or prevent any cardiovascular disease in any animal and/or human in need thereof. In addition, the lack of reasonable correlation between intramuscular and/or intradermal injection and any other route of administration in large animals, as evidenced by McCluskie (DNA vaccine review articles), Anderson (DNA therapy review article) and Verma (DNA therapy review article), is indicative of the lack of reasonable enablement of the full breadth of the claimed invention.

Issue of the inverse relations of HDL cholesterol and coronary heart disease (page 7 bridging page 8 of the response)

Applicant's response is found partially persuasive that the totality of the art of record does recognize that low HDL cholesterol contributes to coronary heart diseases. However, the issue of the breadth of the claimed invention as set forth in claim 31 is not overcome by a mere recognition of the inverse relationship between HDL and coronary hear disease. The state of the art of record exemplified by the totality of the art of records remains doubtful about CETP being solely responsible for any cardiovascular disease, and as such, the Gordon reference even considered as a whole does not overcome the remaining outstanding issues as set forth in the above stated office action.

Note the passage cited by the examiner from Gordon does not in any way contradicts applicant's citations of other passages from Gordon. It is apparent that when considered as a whole, the totality of the art of record clearly indicates that neither HDL nor CETP are solely responsible or causative for any cardiovascular disease in human patients, let alone other large animals as embraced by the claimed invention.

Thus, applicants attempt to correlate between a simple contributing factor of low HDL to coronary heart disease and the role of CETP in preventing and/or treating any cardiovascular disease in any animal including humans are not found persuasive, particularly since applicant does not address the factual data and reasoning as set forth by the art of record, which not only includes Gordon but also Luc *et al.* (Database Embase, AN : 97251152, Sang Trombose Vaisseuax, Vol. 9/4, pp. 206-212), Assmann *et al.* (J

of Cardiovascular Pharmacology. 16/Suppl. 9 (S15-S20). 1991). Stein reference (Atherosclerosis. 144. pages 285-301. 1999). Stedronsky. Biochimica et Biophysica Acta – Lipids and Lipid Metabolism. 1210/3. 255-287. 1994. Kunitake et al.. J. Lipid Res. 33:1807-1816. 1992. and Newnham et al.. Biochim. Biophys. Acta. 1044:57-64. 1990. McNamara in the review article of Biochimica et Biophysica Acta 1529. 2000. 310-320. Hayek *et al.*, J. Clin. Invest., 96. pp 2071-2074, 1995. Inazu et al.. N. Engl. M. Med., 323: 1234-1238. 1990. Zhong et al.. J. Clin. Invest. 97:2917-2923. 1996. Hirano et al.. Arterioscler. Thromb. Vasc. Biol.. 17:1053-1059. 1997. Foger *et al.*, The J. of Biological Chemistry. Vol. 274. 52:36912-36920. 1999. Yamashital *et al.*. Atherosclerosis. 152:271-285. 2000. McCluskie *et al.* (Molecular Medicine. 5. pp. 287-300. 1999). *et al.* (Molecular Medicine Today. 1. 8. pp. 364-72. 1995). Feldman *et al.* (J. Clinical Investigation, 95. 6. 2662-71, 1995).

The issue of rabbit models being art-recognized models for treatment of atherosclerosis (page 9 and page 11)

While the examiner concur with applicant's position that in general rabbits models are art-recognized for treatment of heart diseases. however. specifically as to the issue of the nature of the invention. which is drawn to the use of a CETP-based epitope encoded DNA expression vector to inhibit the level of endogenous CETP so as to provide any preventive and/or treatment effect in any patient in need of the treatment. the cited art remains proper in indicating that the CETP rabbit models wherein a DNA vaccine is employed at the time the invention was made can not be reasonably extrapolated to a reasonable predictability in practicing the full breadth of the claimed invention drawn to the use of the claimed DNA vaccine to inhibit endogenous CETP so as to treat any cardiovascular disease in any patient at risk. or suffering such disease.

Applicant's attempt to rebut the passages cited in Assmann is not found persuasive in view of the reasons set forth *suppra.* e.g.. on the basis of the totality of the art of record. the examiner maintains that a skilled artisan. without any undue experimentation. can not reasonably practice the full breadth of the claimed invention as broadly claimed.

Issue of the typo mistake on pages 5-6 with regard to the term "transgenic model" (page 10).

The examine acknowledges that the "transgenic model" should have been typed as "exemplified rabbit model". The office action when read as a whole does acknowledges that example I has been considered and the stated office action does then indicate that applicant's full disclosure including the prior art's work on transgenic mice and exemplified rabbit models are not reasonably extrapolated to the full breadth of the claimed invention.

Issues of selective passages chosen by the examiner do not reflect the state of the art at the time the invention was made.

This issue again has been discussed *suppra*, and the examiner maintains that not only applicant does not address all of the cited arts so as to have a full grasp of the state of the art of the invention was made, the arts that were asserted by applicants as being used improperly by the examiner remain proper within the context of 35 USC 112, first paragraph, especially when read as a whole and together with other arts such as Stein reference (Atherosclerosis, 144, pages 285-301, 1999), Stedronsky, Biochimica et Biophysica Acta – Lipids and Lipid Metabolism, 1210/3, 255-287, 1994, Kunitake et al., J. Lipid Res. 33:1807-1816, 1992, and Newnham et al., Biochim. Biophys. Acta, 1044:57-64, 1990, McNamara in the review article of Biochimica et Biophysica Acta 1529, 2000, 310-320, Hayek *et al.*, J. Clin. Invest., 96, pp 2071-2074, 1995, Inazu et al., N. Engl. M. Med., 323: 1234-1238, 1990, Zhong et al., J. Clin. Invest, 97:2917-2923, 1996, Hirano et al., Arterioscler. Thromb. Vasc. Biol., 17:1053-1059, 1997, Foger *et al.*, The J. of Biological Chemistry, Vol. 274, 52:36912-36920, 1999, Yamashital *et al.*, Atherosclerosis, 152:271-285, 2000, McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999), *et al.* (Molecular Medicine Today, 1, 8, pp. 364-72, 1995), Feldman *et al.* (J. Clinical Investigation, 95, 6, 2662-71, 1995).

In this regard, it is reiterated that the totality of the art of record does indicate:

1/ Zhong et al., J. Clin. Invest. 97:2917-2923, 1996, Hirano et al., Arterioscler. Thromb. Vasc. Biol., 17:1053-1059, 1997, both tested the hypothesis by performing large population-based studies in Honolulu and Japan, and come up the completely different conclusions by indicating that **low CETP plasma levels due to a common genetic polymorphism as well deficiency of CETP are associated with an increased incidence of coronary heart disease**.

2/ Yamashital *et al.*, Atherosclerosis. 152:271-285. 2000. states:

The deficiency of CETP causes various abnormalities in the concentration, composition, and function of both HDL and low density lipoprotein (LDL). The significance of CETP in terms of atherosclerosis had been controversial. However, the in vitro evidence showed large CE-rich HDL particles in CETP deficiency are defective in cholesterol efflux. Similarly, scavenger receptor BI (SR-BI) knockout mice **show a marked increase in HDL-cholesterol but accelerated atherosclerosis** in atherosclerosis-susceptible mice. Recent epidermiological studies in Americans-Americans and in Omagari area where HALP [hyperalphalipoprotienemia] subjects with the intron 14 splicing defect of CETP gene are markedly frequent, have demonstrated in an **increased incidence of coronary atherosclerosis in CETP-deficient patients** (abstract).

Serum HDL-cholesterol level does not correlated with anti-atherogenicity (page 273, column 2). However, a careful prospective study on the atherogenicity of patients with CETP deficiency is necessary to drawn conclusions. It is also essential to determine clearly whether the increase in HDL-cholesterol may protect against or rather accelerate atherosclerosis in CETP-deficient patients (page 280, column 2).

To the authors' current knowledge, the level of serum HDL may not necessarily imply the functional aspects of HDL particles. HALP may be a condition of an impaired reverse cholesterol transport system. The 'dysfunctional HDL particles' produced by the impairment of molecules involved in reverse cholesterol transport system may lead to the acceleration of atherosclerosis in humans. For this reason, CETP inhibitors may not be a good tool for the purpose of treatment of atherosclerosis. Taken together, it may be important to establish a strategy to assess the efficiency of reverse cholesterol transport system rather than merely determining the level of HDL-cholesterol. (page 280 bridging page 281).

McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees.... and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs, *emphasis added*). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

As such, it is apparent that applicant's response is not found persuasive in view of the all of the reasons set forth above.

No claim is allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette. 1096 OG 30 (November 15. 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632